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THE PATHOLOGICAL ASPECTS OF RHEUMATIC FEVER*

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ALTHOUGH rheumatic fever is still considered a disease of undetermined origin, most authorities believe that it is infectious. Furthermore, many feel that it is closely related to streptococcal infections. There is also much evidence[1,2,3] to suggest that the disease is one of hypersensitiveness to some antigen, probably bacterial.

The widespread changes produced by rheumatic infection throughout the body are now considered to be intimately related even though the etiologic agent cannot be demonstrated in the involved tissues. The inflammatory lesions, although primarily of two types, namely exudative and proliferative, are not sharply limited and vary somewhat with the organ involved.

It is now recognized that the initial lesion of rheumatic fever originates in the supporting structures and the mesenchymal ground substance of the involved organ or tissues. The response to this injury includes edematous swelling of the collagen and elastic fibers with cen-

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tral necrosis accompanied by infiltration of a substance, probably fibrin, which is eosinophilic in staining affinity. The process has been labeled fibrinoid degeneration or swelling[3] (Klinge's "Frühinfiltrat").

Following the injury to the collagen, edema appears in the surrounding tissues, either widespread as seen in the inflamed joints, or local as in the subcutaneous nodules. Numerous polymorphonuclear leukocytes are also present throughout the involved area. These initial reactions are mainly exudative, irrespective of whether they occur in the joints or in the heart valves. Later, proliferating cells appear in these areas of altered collagen. They are rather large cells with basophilic cytoplasm like that of plasma cells, somewhat polygonal in shape and with irregular margins. Their nuclei are vesicular, deeply stained, and with prominent nucleoli. They may be multinucleated especially as seen in the myocardium as constituents of the Aschoff body.

McEwen's[4,5] studies of these cells as obtained at biopsy from subcutaneous nodules and with supravital staining, indicate that they are not phagocytic. He feels that they originate from primitive connective tissue (mesenchymal) cells. With ageing they become longer, produce more collagen and assume the characteristics of fibroblasts.

Joints: Since clinically one of the commonest manifestations of rheumatic fever is polyarthritis, we shall first consider the pathological changes in the joints. The inflamed joint presents both edema of the periarticular tissues and effusion into the cavity causing the swelling, heat and redness found at the bedside. The effusion consists of a gray or yellow turbid mucoid exudate, the cellular content of which usually contains innumerable polymorphonuclear leukocytes, both fresh and degenerating, and a few lymphocytes and monocytes. Bacteria have not been consistently demonstrated in the exudate.

Histologic study of the joints shows practically all of the characteristic rheumatic changes. There is early a diffuse lesion involving the synovia and its supporting tissue. Edema and wandering cells are among the initial changes. Swollen, palisaded, synovial cells may be seen as well as areas of focal necrosis. Fibrinous (fibrinoid) infiltration may involve the superficial layers of the synovia or penetrate into the joint capsule itself.

Later these involved areas are invaded by mononuclear cells. Since they are often arranged perivascularly and in spindle formation they closely resemble myocardial Aschoff bodies.

Less conspicuous, but demonstrable in active cases, are similar granulomata of various ages in the supporting periarticular tissues, the ligaments, aponeuroses, and even where tendons fuse with the periosteum. These arthritic and periarthritic alterations usually heal with no or little permanent damage to the joints.

Subcutaneous Nodules: These interesting manifestations of the rheumatic type of inflammation, encountered chiefly in children, are usually found in areas of physiological stress and strain; for example, in the vicinity of flexor-extensor joints. Grossly they differ considerably depending mainly on their age. At biopsy the younger are soft and jelly-like in consistency with ill-defined margins; the older nodules are firm, gray, fibrous-looking and well circumscribed.

Histologically, the findings also vary with the age of the nodules. In the early stages one finds foci of swollen collagen, some undergoing fragmentation with deposits of fibrinous material and edema fluid in which varying numbers of wandering cells may be sparsely scattered. Blood vessels may show swollen endothelium and other damage; there are microscopic hemorrhages. Surrounding them are collections of polymorphonuclear leukocytes, lymphocytes and typical granuloma cells.

Subsequently there is a gradual organization of the lesion with replacement by fibrous tissue, merging imperceptibly with the original supporting connective tissue. The granuloma cells become elongated, contain less cytoplasm and are separated by layers of newly formed collagen. Lymphocytes and plasma cells are scattered about. The tissue becomes less vascular, more intercellular collagen is deposited, many fibroblasts appear and, finally, only a fibrous scar remains.

Serous Cavities: Involvement of the serous membranes, other than the pericardium, in rheumatic fever is mainly of clinical interest because of the relative infrequency with which active lesions are found at necropsy. As in the case of the joints, the inflammatory process usually resolves completely and thus leaves no residual evidence of its previous existence. Therefore, they are apt to be found at necropsy only in those patients dying during an acute or subacute phase of rheumatic fever in which death is uncommon. However, their incidence would probably be greater at postmortem if they were more carefully sought in these acute cases.

Peritoneum: A focal peritonitis may be found in rheumatic fever. The lesion observed varies from that of fibrinous infiltration to typical

granulomata, particularly in the peritoneum covering the diaphragm and liver, less so in the perisplenic layer. The diaphragm itself is not infrequently the site of rheumatic lesions including fairly typical Aschoff nodules. The psoas muscle has also been described as showing involvement by the rheumatic process.

The peritoneum may also be involved indirectly by lesions produced in the gastrointestinal tract secondary to inflammation of blood vessels supplying this system.

Pleurae: The incidence of rheumatic pleuritis, as encountered clinically, has been given as from 3 to 10 per cent. No figures are available as to its incidence at postmortem but it is probably distinctly less, particularly if only the active lesions are included.

Focal or widespread areas of rheumatic inflammation may be seen in the pleura which resemble the pericardial lesion to be described later. At first a plastic type of exudate is met with but fluid soon makes its appearance. The effusion is turbid, and occasionally blood-tinged. Microscopically, considerable fibrin, desquamated cells, many polymorphonuclear leukocytes and only a few lymphocytes may be seen. McEwen[6] not only found a fairly high percentage of clasmatocytes and undifferentiated young connective tissue cells in pleural exudates, but also, and probably of more importance, a goodly proportion of desquamated mesothelial cells, singly and in groups. The fluid becomes absorbed leaving organizing exudates and causing the pleura to become thickened. Occasionally the fibrinous exudation between the parietal and visceral layers is replaced by fibrous tissue and permanent adhesions between the two layers thereby occur.

Lungs: The existence of a specific rheumatic pneumonia is still a subject for dispute, both clinically and pathologically. There are obvious reasons for this. In the interpretation of the pulmonary changes occurring in patients with rheumatic fever several difficulties arise including the presence of passive hyperemia of the lungs, atelectasis, and the co-existence of unrelated infective pneumonia. At the bedside these changes in the lungs in rheumatic fever may be readily missed since they are transient and rarely produce symptoms or any obvious change in the clinical picture. They consist mostly of migratory areas of focal pulmonary hemorrhage and consolidation and are seen only in the acute or subacute phases of rheumatic infection. Since death in these stages is not common and, since the lesions are usually transient, their

incidence at necropsy is low. Although many pathologists agree on the type of pathological lesions found, there is considerable disagreement as to their specificity.

In the early stages it is thought by some[3,7] that focal hemorrhages of non-specific inflammatory origin are the main lesions. Others[8,9,10] feel that there are more specific changes including a perivascular pneumonia which is considered to be closely related to perivascular lesions. There have been described areas of focal interstitial necrosis and perivascular hemorrhages extending into the alveoli and accompanied by leukocytes of all types. This is associated with a proliferation of interstitial and perivascular cells which is said to resemble that seen in the rheumatic granulomata already described. This reaction together with the vascular lesions and focal hemorrhages constitute what is said to be characteristic of a "rheumatic pneumonia." A final decision regarding the specificity of these changes is still to be rendered. In our experience in the Pathological Laboratories at Bellevue Hospital we have not encountered a satisfactory example of rheumatic pneumonia.

Vascular lesions: Widespread inflammatory changes in blood vessels of all types are now recognized as an important feature in rheumatic fever, Klotz,[11] VonGlahn and Pappenheimer,[12] Holsti,[13] and others have contributed freely to this subject. Rheumatic arteritis may involve the aorta, the pulmonary artery and its branches, the coronary arteries and also the small vessels in the viscera and in the periphery. However, when affecting the smaller arteries the process is recognized histologically only when other rheumatic lesions are present elsewhere, for in itself it is not specific for rheumatic fever. In medium-sized arteries it may resemble polyarteritis nodosa fairly closely, whereas in the aorta and pulmonary artery syphilis is the disease which simulates it.

Rheumatic aortitis is usually only detected histologically but occasionally the presence of yellowish, translucent intimal plaques in the root or the ascending portion of the aorta, or at the root of the pulmonary artery, may suggest its presence, particularly if other rheumatic lesions are also present.

In the acute or active phases the intimal changes consist of swelling of fibrils and proliferation of large mononuclear cells arranged in rows between elastic or collagen tissue bands. In the media focal collections of polymorphonuclear leukocytes may collect between degenerating muscle and elastic fibers. In the adventitia granuloma cells and poly-

morphonuclear leukocytes may be seen about the vasa vasorum and even discrete Aschoff nodules may form. The vasa vasorum may also present inflammatory changes. In the healed stage only dense avascular flame-shaped scars are seen in the vicinity of the vasa vasorum. The latter may show distinctly thickened walls and stenotic lumina.

Coronary arteritis is usually not recognized grossly in the acute phase. In the healed stage there may be thickening of the artery and stenosis of its lumen of sufficient degree to be seen with the naked eye.

Histologically, polymorphonuclear leukocytes and large cells with pyknotic nuclei infiltrate the swollen coats of the affected vessels. The endothelium is often raised by a subintimal deposit of fibrin. The media may undergo necrosis, and hemorrhage may separate the muscle fibers. The inflammatory cells may form perivascular collars in the adventitia. Thrombosis and aneurysm formation are extremely rare. When healing takes place there results an irregular growth of connective tissue in all three coats with a resultant nodular thickening of the vessels. At times it is difficult to differentiate the lesion from that of atherosclerosis.

In addition to the vessels just considered many types of rheumatic changes have been described[12,13] in the arteries in other portions of the peripheral vascular tree. The arteritis may involve one or all of the layers of the vessels. One of the simplest changes noted is mere swelling of the endothelium, in others it may be separated from the basement membrane by a structureless fibrin-like material. There may be fragmentation of the elastic tissue or the media may show areas of fibrinous infiltration. Occasionally the process extends to the adventitia with infiltration of polymorphonuclear leukocytes and red blood cells into the perivascular tissues. In this stage the appearance is very much like polyarteritis nodosa.[14]

Heart

Although I have kept the consideration of the heart and its lesions for the end of this presentation, it is by far the most important organ involved in rheumatic fever. It not only is responsible for the majority of deaths in this disease but is also the seat of most of the physical disability sustained by those affected.

Carditis is the chief visceral manifestation of rheumatic fever. Although in the correct sense of the term it signifies inflammation of the whole heart, through clinical usage it has become to mean involvement

of any portion of the organ. The myocardium and the valves are the structures involved in the majority of instances; more rarely the pericardium. The more severe the rheumatic inflammation the more likely are all three structures to be involved.

Heart valves and Endothelium: In the pathogenesis of valvular lesions in rheumatic fever emphasis is now placed on the primary involvement of the substance of the valve rather than on the implantation of the infectious agent on its surface. As shown by Gross,[15] Holsti[16] and others, there is a close relationship between the left auricle, the pericardial wedge adjacent to the annuli of the valves, the valve rings and the valve leaflets. This probably furnishes the correct interpretation of the initial process, namely, that the primary inflammation is in the valve substance (interstitium) with secondary changes on the surface epithelium leading to the formation of rheumatic vegetations. It has therefore been recommended[17] that the term "valvulitis" be employed to denote the endocardial changes occurring in the valves in rheumatic fever when accompanied by diffuse changes in the valve substance.

Others[18] have considered the first injury to be endothelial, recognizing that the endocardium is specially subject to physiological trauma, particularly at the line of closure where the cusps impinge. However, at this point it is well to mention that Swift,[19] Holsti[16] and others have described cases with marked interstitial valvular inflammation without verrucous lesions, usually in patients dying accidentally while in an early phase of the disease.

Small, firm, gray or pinkish gray verrucae along the line of closure of the leaflets, most often on the mitral and aortic valves, constitute the commonest lesion seen by the naked eye in active rheumatic valvulitis. Histologically the verrucae appear as pink-staining material protruding from the leaflet, denude of endothelium. The eosinophilic material usually extends into the swollen interstitium of the leaflet. Fibrin may be deposited on the superficial aspects of the verrucae. Where the verruca meets connective tissue, variable changes may be seen. Prominent are large mononuclear cells with basophilic cytoplasm, some elongated, and at times arranged in palisades at right angles to the surface of the valve. Polymorphonuclear leukocytes and eosinophiles are less prominent.

In addition, as previously mentioned, diffuse interstitial inflammation may be seen in the leaflet without verrucae or other changes being

visible grossly. Small vessels at the base of the leaflet are increased in number and protrude into the valve. The collagenous tissue is edematous and invaded by polymorphonuclear leukocytes and eosinophiles. Rarely Aschoff bodies may appear in the valve substance near the vessels. The valve rings usually present the same changes.

Since patients with rheumatic fever rarely die in the first episode, hearts presenting only acute or active lesions are seldom encountered at necropsy. The leaflets in rheumatic hearts usually exhibit combinations of fresh and healed lesions, suggesting the presence of a chronic active valvulitis or a recurrent inflammation in a previously damaged valve. Verrucae discernible on the edge of the deformed leaflets are evidence of an active process. In other instances signs of active inflammation may be only microscopic.

The main feature of the healing process in the valves is an increase of connective tissue elements with scarring. The leaflets are opaque, of limited mobility and fused at their junctions. The healed verrucae may leave a fibrous ridge along the line of closure. The semilunar cusps become shorter and the orifices enlarge. Where fusion of cusps occurs stenosis of the orifice develops. The chordae tendineae are thickened, especially at their insertion, and often they fuse together or with the papillary muscles. The valve leaflets become immobile, and stenosis of the orifices and insufficiency of the valves ensue. Capillaries and calcific deposits may be visible beneath the endothelium of the scarred valve. Ulceration may result when these calcific deposits lie close to the surface endothelium. Bland thrombi may be deposited, especially when the auriculo-ventricular valves are so involved.

In some instances, probably infrequent, the exudative phenomena may recede and leave little evidence beyond the presence of changes similar to those occurring in advancing age, or only localized areas of a healed valvulitis.

MacCallum[20] was the first to describe the mural endocarditis which occurs so frequently in the left auricle. It consists of grayish-yellow corrugations of the endocardium localized, as a rule, to the area just above the posterior mitral leaflet. It is of importance since it not infrequently acts as a nidus for the implantation of bacterial endocarditis.

In these cases the endocardium and subendocardium are infiltrated by eosinophiles, polymorphonuclear leukocytes and many distorted cells with crescentic or elongated nuclei arranged perpendicularly to

the endocardium. Beneath this reaction are present long bands of elastic tissue or swollen collagen, along which large granuloma cells ("Aschoff" cells) are arranged in palisades. Spindle-shaped Aschoff nodules are fairly frequent in the active stages of mural endocarditis.

As the process becomes chronic, endocardial reduplications develop with increased vascularity of the subendocardial layers and often hypertrophy of the auricular myocardium.

At this point it might be pertinent to say a word about mural thrombosis, particularly in view of the fact that active rheumatic inflammation may frequently be seen in the underlying auricular tissue.[21] Thrombus formation is most commonly confined to the left auricle or its appendage; less frequently in the right auricle and appendage, or bilaterally. Intraventricular thrombi are rarely encountered in rheumatic hearts.

Certain factors apparently favor the development of auricular thrombi. These include severe mitral stenosis together with congestive heart failure, auricular fibrillation and continued local inflammation.[21,22] Of these, the persistence of active inflammation in the auricular endocardium appears to be the main one.

Myocardium: Rheumatic myocarditis presents no gross features other than dilatation and occasionally hypertrophy. The characteristic lesion, only visible microscopically, is the submiliary nodule described by Aschoff in 1904 and which remains the most specific lesion of rheumatic fever. The Aschoff node forms about foci of swollen and fragmented collagen in the perivascular connective tissue and in the interstitial tissue between muscle bundles. Edema and exudation of polymorphonuclears are among the early changes. Later there appear the characteristic granulomata cells previously described, with abundant granular, basophilic cytoplasm, conspicuous nuclei and prominent hyperchromatic nucleoli. Some are large and multinucleated ("Aschoff" cells).

Aschoff nodules may be found anywhere in the myocardium but the sites of greatest frequency are (1) interventricular septum, (2) wall of left ventricle, (3) papillary muscles, and (4) in the wall of the left auricle.

During the healing stage the Aschoff body contains many lymphocytes and fibroblasts and finally a minute perivascular fibrous scar remains. Occasionally the acute inflammatory reaction may be wide-

spread. Leukocytes may collect near Aschoff nodules but may also be found throughout the interstitial tissue of the myocardium or at the margins of miliary foci of necrosis.

More common than uncomplicated acute rheumatic myocarditis is chronic active myocarditis, for even those patients dying in the course of an apparently first episode, may show healed or organizing lesions as well as fresh ones. Histologically the co-existence of healing or healed perivascular and interstitial miliary scars with Aschoff bodies in various stages of development is the striking feature of this type of rheumatic inflammation.

Pericardium: The early lesions of rheumatic pericarditis are usually found over the base of the heart, near the origin of the great vessels. There may be seen a layer of shaggy, yellowish fibrin covering the pericardial surfaces. When extensive it gives the appearance of the so-called bread and butter heart. Effusion is seldom excessive and rarely purulent. However, it commonly is sanguineous.

The histological recognition of the process is dependent largely on the finding of rheumatic lesions elsewhere in the heart. One reason for this is the fact that Aschoff bodies are only occasionally found in the pericardium. Few polymorphonuclear leukocytes are present in the exudate. The endothelium beneath the fibrinous exudate may be swollen but otherwise fairly well preserved. In the deeper portions there may be seen a proliferation of fibroblasts and endothelial sprouts and also new vessel formation. The latter may bleed, thereby causing the sanguineous character of the exudate.

Mild rheumatic pericarditis may heal without leaving any visible scar. Occasionally, localized areas of thickened pericardium resembling "milk patches" may be the only residue of previous rheumatic inflammation. In other cases the entire visceral pericardium is thickened although smooth and glistening. Fibrous adhesions between the pericardial layers are another end-result of organization. They may be localized or obliterate the entire pericardial sac. Adhesions may also bind the pericardium to neighboring structures, particularly to the mediastinum. However, it is of interest to note that rheumatic pericarditis rarely, if ever, produces a constrictive type of adherent pericardium.

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